

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75184

CORRESPONDENCE

ANDA 75-184

AUG 28 2000

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M. Viti, Ph.D.
4400 Biscayne Blvd.
Miami, FL 33137

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL (packaged in 30 mg/5 mL, 150 mg/25 mL, and 300 mg/50 mL multiple-dose vials).

Reference is also made to your amendments dated June 23, July 14, July 25, August 7, August 8, August 21, August 22, and August 24, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

The listed drug product (RLD) referenced in your application, Taxol Injection of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on August 3, 2012, [U.S. Patent No. 5,641,803 (the '803 patent), and U.S. Patent No. 5,670,537 (the '537 patent)], March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 patent)], and February 22, 2013 [U.S. Patent No. 6,096,331 (the '331 patent)]. Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the '803, '537, or '331 patents. In addition, your application contains a patent statement under Section 505(j)(2)(A)(viii) of the Act indicating that the '804 patent is a method of use patent, and

that this patent does not claim any of the proposed indications for which you are seeking approval. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the owner of the new drug application (NDA) for the referenced listed drug product and the patent holder. You have notified FDA that Baker Norton Pharmaceuticals, Inc. complied with the requirements of Section 505(j)(2)(B) of the Act with respect to the '803 and '537 patents. As a result, Bristol-Myers Squibb Co. initiated a patent infringement suit involving these patents against Baker Norton Pharmaceuticals, Inc. and Ivax Corporation in the United States District Court for the District of New Jersey (Bristol-Myers Squibb Company v. Baker Norton Pharmaceuticals, Inc. and Ivax Corporation, Civil Action No. 97-6050). You have also notified the Agency that with respect to the suit mentioned above, the 30-month period during which the Agency was precluded from approving this application expired on June 2, 2000. Thus, final resolution of the approval status of this application can not be concluded until all legal and regulatory issues surrounding your challenge of the '331 patent have been satisfactorily resolved.

In order to reactivate your application prior to final approval, please submit an amendment at least 60 days prior to the date you believe the application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing and controls data as appropriate. Alternatively, a statement should be provided stating that no changes have been made to the term of the application since the date of this tentative approval letter. In addition, the final disposition of your certification to the '331 patent should be submitted. This amendment should be designated clearly in your cover letter as a MINOR amendment. In addition to, or instead of this amendment, the Agency may request at any time prior to the date of final approval of this application that you submit an amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to the Agency review before final approval of the application will be made.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

Prior to submitting the amendment(s), please contact Elaine Hu, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

02

ANDA 75-184

Immunex Corporation
Attention: Nancy Kercher
51 University Street
Seattle, Washington 98101-2936

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Dear Madam:

After careful review, the Office of Generic Drugs has decided to rescind our "Refuse to File" letter dated September 3, 1997. Accordingly, the application is accepted for filing.

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your correspondence dated September 26, 1997.

NAME OF DRUG: Paclitaxel Injection, 6 mg/mL, 5 mL vial

DATE OF APPLICATION: July 30, 1997

DATE OF RECEIPT: August 8, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-184
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/Prickman, Chief, RSB _____ date
HFD-615, GDavis, CSO _____ date
HFD-625, MSmela, Sup. Chem. _____ date

ANDA Acknowledgment Letter!

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ANDA 75-184

Immunex Corporation
Attention: Nancy Kercher
51 University Street
Seattle, Washington 98101-2936

SEP 3 1997

|||||

Dear Madam:

Please refer to your abbreviated new drug application dated July 30, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act (the Act) for Paclitaxel Injection, 6 mg/mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

Your proposed formulation contains an inactive ingredient that has not been previously approved in a parenteral drug product for human use.

21 CFR 314.94(a)(9)(iii) allows an applicant to seek approval of a parenteral drug product that differs from the reference listed drug in a buffer, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product. We acknowledge your explanation to support safety through reasoning that the previous approval and use of (each a separate inactive ingredient) could lead to a conclusion that is safe.

The Associate Director for Medical Affairs in the Office of Generic Drugs (OGD) has reviewed your documentation and does not concur with your conclusion that can be considered safe without reservation.

Under 21 CFR 314.101(d)(2), FDA may refuse to file an ANDA or not consider an ANDA to be received, if the abbreviated

application is not submitted in the form required under section 314.94. Similarly, FDA may refuse to file an ANDA, or not consider an ANDA to be received, if the abbreviated application is incomplete because it does not on its face contain information required under Section 505, Section 505(j) or Section 507 of the Act, and 21 CFR 314.50 or 314.94.

As noted above, Section 314.94(a)(9) governs inactive ingredients for ANDA's. In addition, Section 314.127(a)(8)(ii) provides that FDA may refuse to approve an ANDA if there is a reasonable basis to conclude that one or more of the inactive ingredients raises serious questions of safety. Furthermore, 21 CFR 314.127(a)(8)(ii)(A)(3) states that FDA will refuse to approve an abbreviated application if an inactive ingredient in a proposed parenteral drug product has not been previously approved in a parenteral drug product. Therefore, this application cannot be approved as an ANDA under section 505(j) of the Act. Thus, if FDA determines that it would refuse to approve an ANDA because, in the Agency's view, one or more inactive ingredient raises serious questions of safety, FDA may refuse to file the ANDA.

You should consider either reformulating your proposed drug product or seek approval under section 505 (b) of the Act. If you wish to seek approval under section 505(b) we recommend that you contact the Division of Oncologic Drug Products regarding the requirements for filing the application as an NDA.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter, you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3).

If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions concerning this letter please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research .

DW

ANDA 75-184

SEP 18 2000

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M. Viti, Ph.D.
4400 Biscayne Blvd.
Miami, FL 33137

Dear Sir:

On September 15, 2000, Baker Norton Pharmaceuticals, Inc. (BNPI) received approval for an abbreviated new drug application (ANDA) for Paclitaxel Injection, 6 mg/mL. The purpose of this letter is to clarify the 180-day exclusivity provisions under the Federal Food, Drug, and Cosmetic Act with respect to your application. In light of the recent court decisions in Granutec v. Shalala, and Mova v. Shalala, including the district court's order of June 1, 1998 in Mova, declaring the "successful defense" requirement 21 C.F.R. 314.107(c)(1) invalid, and directing FDA not to enforce it, FDA is reinterpreting Section 505(j)(5)(B)(iv).

A review of the agency's records reveals that BNPI was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification to U.S. patents 5,641,803 and 5,670,537 for the drug product noted above. You were sued as a result of the notice you provided to the holder of the NDA and the patent owner. Approval of your application was based upon the expiration of the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act. Thus, BNPI is eligible for 180-days of market exclusivity for this drug product. Such exclusivity will begin to run either from the date BNPI begins commercial marketing, or from the date of a decision of a court finding the patent invalid or not infringed, whichever occurs earlier [Section 505(j)(5)(B)(iv)]. A court decision that can trigger the beginning of exclusivity is a decision of any court in a patent infringement action resulting from a Paragraph IV Certification in which the court finds that the patent is invalid or not infringed. With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 C.F.R. 107(c)(3) and (4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner.

If you have additional questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710) or contact Mr. Donald Hare, Special Assistant to the Director, at (301) 827-5845.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research



September 26, 1997

Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-184
Paclitaxel Injection
Patent Certification for Paclitaxel Injection

Dear Mr. Sporn:

Per your request attached please find a revised Patent Certification for Paclitaxel Injection.

If you have any questions regarding this information, please contact me at (206) 389-4095.

Sincerely,

Nancy L. Kercher
Director,
Regulatory Affairs
Immunex Corporation

NEW CORRESP

*NI
Patent certification
PI w/ qualifying
language. Accepted
W. Kercher
9/26/97*

RECEIVED

SEP 26 1997

GENERIC DRUGS





*NAI
mmh
12/8/97*

November 26, 1997

NEW CORRESP.

NC

Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-184
Paclitaxel Injection
Patent Certification for Paclitaxel Injection

Dear Mr. Sporn:

Attached please find Patent Certification for Paclitaxel Injection.

If you have any questions regarding this information, please contact me at (206) 389-4095.

Sincerely,
Mark W. Kercher
Nancy L. Kercher
Director,
Regulatory Affairs
Immunex Corporation

RECEIVED

NOV 28 1997

GENERIC DRUGS

*Mark
12-1-97*





December 1, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: ANDA 75-184, Amendment No. 1
Paclitaxel Injection
Patent Certification and Exclusivity Statement**

Dear Mr. Sporn:

We wish to amend our unapproved application for Paclitaxel Injection to revise Section III, Patent Certification and Exclusivity Statement, to add reference to Patent No. 5,670,537, which was previously not included in Section III. We have also modified the language to specify that "We certify that on November 26, 1997 Immunex notified Bristol-Myers Squibb Company pursuant to 21 CFR 314.95(a) and that such notification met all of the requirements of 21 CFR 413.95(c)."

If you have any questions regarding this information, please contact me at (206) 389-4095.

Sincerely,

Nancy Kercher
Director,
Regulatory Affairs

*needs
copy of return receipt
to show proof of notification.
Winkman
11/5/98*

*NEW BUSINESS?
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DEC 02 1997
GENERIC DRUGS**



*Nachwe
12-8-97*

Spoke w/ Nancy Kercher 2/3/98



this letter was sent before Immunex was served notice in

January 13, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

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NAI
AS 2/3/98
Angry Darts

**RE: ANDA 75-184, Amendment No. 2
Paclitaxel Injection**

Dear Mr. Sporn,

This is to notify the Food and Drug Administration that Bristol-Myers Squibb Company ("BMS") was provided notice pursuant to 21 U.S.C. §355(j)(2)(B)(ii) by telefax on November 26, 1997. Enclosed is a copy of a letter from BMS acknowledging receipt of Immunex's November 26, 1997 letter. Also enclosed is the transmission report indicating that the telefax was successfully transmitted to BMS on November 26, 1997. We further enclose a copy of the return receipt that confirms BMS' receipt on December 2, 1997 of the certified mail copy of Immunex's letter.

Based on the documentation, copies of which are provided with this letter, BMS was provided a full copy of the notice on November 26, 1997. As of the date of this letter, BMS has failed to bring an action for patent infringement within 45 days after November 27, 1997. Therefore, Immunex has satisfied all requirements as specified in 21 CFR §314.95, and the effective date of the approval of ANDA 75-184 is no longer contingent on the outcome of any patent infringement litigation. We therefore request timely review and approval of this ANDA.

If you should have any questions regarding this information, please contact me at (206) 389-4095. I will contact you by phone within the next few days to follow-up on this communication.

Sincerely,

Mark W. Spentini

Nancy L. Kercher
Director,
Regulatory Affairs

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JAN 18 1998

GENERIC DRUGS

*Nancy Kercher
1-16-98*





Bristol-Myers Squibb Company

PO BOX 4000, PRINCETON, NJ 08542-4000
609 271 4528 FAX 609 271 4729

January 19, 1998

NEW CORRESP

ME

Donald J. Barrack
Chief Counsel - Patent

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

NAT 2/3/98
Angus S. Davis

RE: Bristol-Myers Squibb Company v. Immunex Corporation

Gentlemen:

ANDA 75-184 filed by Immunex Corporation ("Immunex") is directed to its paclitaxel injection generic version of Bristol-Myers Squibb's ("BMS") Taxol® and contains a certification under 21 U.S.C. §355(j)(2)(A)(vii)(IV) asserting that United States Patents No. 5,641,803 and 5,670,537 are invalid and unenforceable. Notice of the certification was received by BMS by certified mail on December 2, 1997. A courtesy copy of the notice was sent to BMS via facsimile by Immunex on November 26, 1997.

This letter is to advise the Food and Drug Administration ("FDA") that on January 8, 1998, BMS filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537. A copy of the complaint is enclosed (Civil Action No. 98-159 (DRD), United States District Court, District of New Jersey).

BMS has filed its action within 45 days of receipt of notice of the certification, and pursuant to the Federal Food, Drug and Cosmetic Act ("FFDCA"), §505(j)(4)(B)(iii), the FDA cannot approve ANDA 75-184 until "the expiration of the thirty (30) month period beginning on the date of the receipt of the notice. . . or such shorter or longer period as the court may order" Because Immunex provided notice of its patent certification to BMS prior to the expiration of the five (5) year data exclusivity period enjoyed by BMS pursuant to FFDCA §505(j)(4)(D)(ii), the thirty (30) month period is "extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of [BMS's paclitaxel new drug application]".

Should any questions concerning this matter arise, please feel free to contact me directly.

Sincerely,

[Handwritten signature]

RECEIVED

JAN 21 1998

GENERIC DRUGS

IMMUNEX

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JUL 01 1998

GENERIC DRUGS

June 30, 1998

Douglas Sporn
Director, Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

LEVI COURTESY

NC

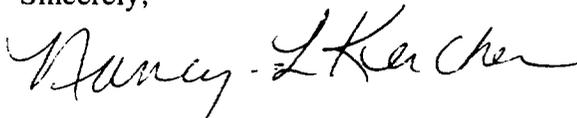
RE: ANDA 75-184
Paclitaxel Injection
Update Regarding Deficiency Letter

Dear Mr. Sporn:

This is to advise you that I will be contacting Mr. Joe Buccine the week of July 13, 1998 to arrange a meeting to obtain clarification regarding a few of the questions in our March 6, 1998 Deficiency Letter. I would also like to acknowledge receipt of Mr. Joseph Buccine's message confirming the Pharmacology/Toxicology consult of our October 7, 1997 submission is complete and that there are no additional questions. Formal responses to the Deficiency Letter will be submitted after the above referenced meeting.

If you should have any questions concerning this information, please contact me directly at (206) 389-4095.

Sincerely,



Nancy L. Kercher
Director,
Regulatory Affairs
Immunex Corporation

Handwritten signature and date: 7-6-98



NEW CORRESP

NC

August 20, 1998

Dr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Paclitaxel
ANDA 75-184
General Correspondence
Change in Ownership

Dear Dr. Sporn,

We hereby notify you of the transfer of ownership of Abbreviated New Drug Application 75-184 for Paclitaxel, 6mg/mL in 5 mL (30 mg), from Immunex Corporation to Baker Norton Pharmaceuticals, Inc., 8800 N.W. 36th Street, Miami, FL 33178-2404, effective August 21, 1998.

ANDA 75-184 was received by FDA on August 8, 1997. The ANDA is currently under review by the Office of Generic Drugs.

Effective August 21, 1998, all rights to ANDA 75-184 have been transferred to Baker Norton Pharmaceuticals, Inc.

Immunex Corporation has provided Baker Norton Pharmaceuticals, Inc., with a complete copy of the Abbreviated New Drug Application. If you have any comments or questions regarding the transfer of this product, please contact me at (206) 389-4095.

Sincerely,

Nancy L. Kercher
Director, Regulatory Affairs

SEP 21 1998

18

August 20, 1998

NEW CORRESP

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

RE: ANDA 75-184, Paclitaxel Injection

Transfer of Ownership

Dear Mr. Sporn:

Baker Norton Pharmaceuticals, Inc. hereby accepts ownership and all rights to ANDA 75-184 for Paclitaxel Injection. This ANDA, is being transferred from Immunex Corporation. Immunex has submitted to this ANDA a letter of transfer of ownership.

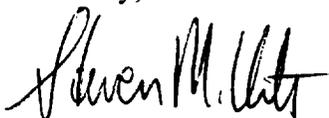
Baker Norton Pharmaceuticals requests a complete copy of the application from FDA's files. The application was filed July 30, 1997 and is pending a deficiency letter response, which will be submitted by Baker Norton Pharmaceuticals. Additionally, we commit to the agreements promises and conditions made by the former owner and contained in the application.

Attached is an updated FDA form 356h indicating the transfer of ownership.

Upon completion of our review of this ANDA, we will request a meeting with OGD to discuss our proposed response to the pending deficiency letter.

Should you have any questions or require further information relating to this transfer, please do not hesitate to contact me at (305) 575-6336 or Fax (305) 575-6339.

Sincerely,



Steve Viti, Ph.D.
Acting Director, Regulatory Affairs

RECEIVED

AUG 21 1998

GENERIC DRUGS

April 2, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/AC

MAJOR AMENDMENT

Dear Mr. Sporn:

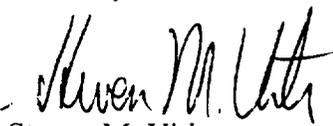
RE: ANDA 75-184
Paclitaxel Injection 30 mg/5 mL, Multiple Dose Vials

Reference is made to the Agency's communication to Immunex Corporation dated March 6, 1998 regarding deficiencies in the above application. Please note that on August 20, 1998, Baker Norton Pharmaceuticals notified the Agency that Immunex had transferred ownership and all rights to ANDA 75-184, and that Immunex had submitted to this ANDA a letter of transfer of ownership. Based on the transfer of ownership from Immunex to Baker Norton Pharmaceuticals, the manufacture of the finished product was transferred to Faulding Pharmaceuticals, and release testing will now be performed at Baker Norton Pharmaceuticals.

Under the provisions of 21 CFR 314.120 and 314.96, Baker Norton Pharmaceuticals hereby amends the above application to provide responses to the deficiencies noted by the Agency. The deficiencies identified by the Agency are shown in boldface, followed by the response. It should be noted that this response describes a revised formulation of the finished product, as recommended by the Agency in Comment #7.

We trust that this Major Amendment responds to the deficiencies identified and all information provided is complete. If you have any questions or require further information, please do not hesitate to contact me at (305) 575-6336. Your time and consideration are greatly appreciated.

Sincerely,



Steven M. Viti
Acting Director, Regulatory Affairs
Baker Norton Pharmaceuticals, Inc.

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APR 05 1999

GENERIC DRUGS

ANDA 75-184
GRATUITOUS AMENDMENT

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

June 15, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

AA

RE: Paclitaxel Injection, 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL
Multiple Dose Vials

Dear Mr. Sporn:

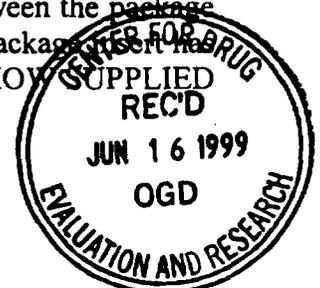
Reference is made to ANDA 75-184 for Paclitaxel Injection, 30 mg/5 mL, Multiple Dose Vials, originally submitted by the Immunex Corporation. As noted in our correspondence to the Agency of August 20, 1998, Immunex has transferred ownership and all rights to ANDA 75-184 to Baker Norton Pharmaceuticals. At the time of ownership transfer, Immunex had on file an outstanding deficiency letter from the Agency dated March 6, 1998.

On April 2, 1999, Baker Norton responded to the Agency's deficiency letter of March 6, 1998. That Major Amendment responded to all of the observations noted by the Agency in their letter of March 6, 1998 and included all information pertinent to the 30 mg/5 mL vial size. We are now amending our response of April 2, 1999 to provide for two additional sizes:

150 mg/25 mL (represented by exhibit batch 8026859); and
300 mg/50 mL (represented by exhibit batch 8016861).

As mentioned above, the two additional vial sizes presented here are in addition to the 30 mg/5 mL vial size already pending with the Agency. It is our intention for the information on these two additional sizes to be reviewed in conjunction with our Major Amendment dated April 2, 1999, and be treated as one complete Amendment.

We acknowledge that our Major Amendment of April 2, 1999 provided a package insert and carton and vial labeling for the 30 mg vial size only. The draft vial and carton labeling for the 150 mg/25 mL and the 300 mg/50 mL strengths presented here are similar in content and format to that previously submitted for the 30 mg/5 mL size. The only difference between the package insert presented here and that provided in our previous amendment is that the package insert has been revised to include the 150 mg/25 mL and the 300 mg/50 mL sizes in the HOW SUPPLIED section.



A list of updated sections of the application follows. Please note that we are submitting at this time only that information which is new or which has changed based on the inclusion of the two additional sizes. There are no changes to the Sterility Validation package submitted in Section XI.5 of our April 2, 1999 Amendment, as validation was based on vial sizes ranging from mL, including container/closure integrity testing by microbial challenge.

It should be noted that an out of specification in-process assay result of % was experienced with exhibit batch 8026859. Final assay was within specification. On February 8, 1999 we discussed this situation with Mr. Joseph Buccine of the OGD (to confirm the appropriateness of submitting it as an exhibit batch); and after consultation with the Review Chemist, Mr. Buccine advised the batch could be submitted as long as an Investigation Report were supplied and a commitment made that the batch would be limited to "exhibit" use only.

ADDITIONAL INFORMATION (Sections 11.3, 13, 14 and 15)

We are also providing the following data at this time, for further clarification of material already presented to the Agency in our Major Amendment of April 2, 1999:

1. Additional data regarding the stability of the paclitaxel product in various intravenous solutions (see Section 11.3).
2. Additional data regarding the use of Citric Acid in the formulation (see Section 13).
3. Additional data regarding the impurity, which appears only in the drug product (see Section 14).
4. Additional data regarding the control of paclitaxel active drug substance molecule (see Section 15).

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to call me at (305) 575-6336.

Sincerely,



Steven M. Viti
Director, Regulatory Affairs
Baker Norton Pharmaceuticals, Inc.

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

June 30, 1999

NEW CORRESP
NC

NAT
9/1/99
Gregory S. Land

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-184
Paclitaxel Injection
Patent Certification and Exclusivity Statement

Dear Mr. Sporn:

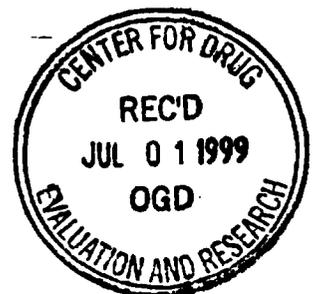
We wish to amend our pending application for Paclitaxel Injection to revise Section III, Patent Certification and Exclusivity Statement, to add reference to Patent No. 5,496,804 and the Exclusivities which were not previously included in the application.

If you have any questions regarding this information, please contact me at (305) 575-6336.

Sincerely,

Julyn Cheney
for Steven M. Viti, Ph.D.
Director, Regulatory Affairs

cc: Mr. Greg Davis (FAX: 301-594-1174)





Telephone 305-575-6004
Fax 305-575-6027
E-mail: jhsiao@ivax.com

Jane Hsiao, Ph.D., MBA
Vice Chairman Technical Affairs

August 19, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

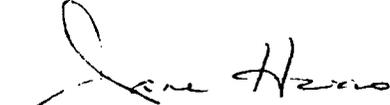
NC
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N

Dear Mr. Sporn:

As a courtesy copy, I am attaching my letter to Margaret Jane Porter, Chief Counsel, Office of the Chief Counsel and Jane Axelrad, Associate Director for Policy, Center for Drug Evaluation and Research for your information.

Best regards.

Sincerely,


Jane Hsiao, Ph.D., MBA
Vice Chairman, Technical Affairs

JH/pq



November 16, 1999

NEW CONCEPT

V.C.

Mr. Douglas L. Sporn
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 286
7500 Standish Place
Rockville, Maryland 20855

Re: 180-Day Exclusivity for ANDA No. 75-184 – Paclitaxel Injection

Dear Mr. Sporn:

Thank you for your September 22, 1999, letter. In it, you declined to respond to Baker Norton Pharmaceuticals' (BNP) request of August 17, 1999, for confirmation that the scope of 180-day exclusivity for BNP's ANDA for paclitaxel injection will extend to all subsequent ANDAs for paclitaxel injection in a dosage strength of 6 mg/ml, irrespective of container size. You suggested that BNP instead submit either a citizen petition or a comment on the FDA's pending proposal to establish a triggering period for 180-day exclusivity.

Attached to this letter is a copy of a citizen petition submitted to the agency by our regulatory counsel. The citizen petition asks the FDA to clarify its suitability petition policy as it relates to ANDAs for a parenteral drug product in a container with a different "total drug content" compared with the container approved for the listed drug. Under the policy, such differences are characterized as differences in "strength." Any artificial limitation on the scope of 180-day exclusivity for the BNP ANDA for 6 mg/ml paclitaxel injection so that it applies only to 5 ml containers will be a result of that policy, and not

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NEW DRUG
1999

the result of the agency's interpretation of the 180-day exclusivity provision. Accordingly, the citizen petition addresses the suitability petition policy.

We decided to submit a citizen petition rather than a comment in the 180-day exclusivity rulemaking proceeding in order to facilitate an expeditious response by the FDA to our request for relief. As I noted in my August 17 request, the 30-month stay on the effective approval date for the BNP ANDA will expire on June 2, 2000. For business planning reasons, it is important for BNP to know well in advance of that date whether or not the FDA will attempt to limit the scope of the ANDA's exclusivity. It is unlikely that BNP's need for a timely resolution of this matter could be met if the agency's response were governed by the schedule for completing the rulemaking proceeding. Additionally, the suitability petition policy focuses on the specific issue of what "strength" means in the context of parenteral drugs. Once "strength" is defined, we believe exclusivity outcomes are obvious.

The citizen petition makes a simple point, specifically, that the "strength" of a parenteral drug in solution form cannot be equated with the "total drug content" of the container in which the drug is supplied. This is obviously correct. No one – from the USP, to pharmacists, to drug manufacturers – views parenteral drug container size as a drug "strength." In fact, other than to require a suitability petition, the FDA itself does not regard the total content of a parenteral drug container as the same thing as the "strength" of the drug in the container. Rather, the "strength" of a ready-to-use parenteral drug is its concentration, that is, the amount of active ingredient in a specified volume unit. The "strength" of any drug is the amount of active ingredient in a specified unit, whether it be a dosage unit, a unit of volume, or a unit of weight. Drug "strength" is never simply the absolute amount of active ingredient in a container or package.

As the citizen petition points out, the FDA could interpret "strength" for parenteral drugs as the amount of active ingredient in a "single-dose" container. It could do this by

characterizing a single-dose container as an appropriate “unit” of the drug, similar to a tablet. In this way, the agency could continue to require suitability petitions for new single-dose parenteral drug container sizes. But for the FDA to require suitability petitions for different multiple-dose parenteral drug container sizes makes no sense. Total active ingredient fill volume for containers not meant to provide a “single dose” of a drug, but simply to supply a quantity of the drug for use by physicians and pharmacists to prepare the dosage unit that will be administered, is not a drug “strength” on the basis of any medical, scientific, or technical authority, or on the basis of any FDA regulation, guidance document, or other source of agency interpretation or precedent – except for the informal suitability petition policy, if it, indeed, applies to multiple-dose parenteral drug containers. (Clearly, people think it applies, because there are suitability petitions relating to multiple-dose containers. But in the absence of an FDA explanation of the specific terms of the policy, or the reasons for it, it is possible that applicants simply assume the policy applies to multiple-dose containers, and the FDA simply accepts and acts on the resulting suitability petitions for the sake of consistency – even though it may never have been the intention of the agency to review multiple-dose container sizes in this way.)

Paclitaxel injection 6 mg/ml is supplied by Bristol-Myers Squibb in multiple-dose containers of several sizes. BNP and subsequent ANDA applicants will offer those sizes, and others. The fill volume of these multiple-dose containers is not, and does not equate with, the “strength” of paclitaxel, which remains 6 mg/ml, no matter the container size. Of course, multiple-dose containers with different fill volumes may be offered in part to provide amounts of paclitaxel closer to those that will be used to make up a dosage unit for a specific course of administration. There are sound, practical reasons why this is done, including convenience of storage and reducing the number of containers that must be opened for a particular treatment. Nevertheless, a multiple-dose parenteral drug container is not a dosage unit, and the “total drug content” of such a container is not a

“strength” of paclitaxel. Therefore, if the FDA does not apply BNP’s 180-day exclusivity to 6 mg/ml paclitaxel injection in all container sizes, it will violate the statute and effectively destroy the value of the 180-day marketing exclusivity BNP will have earned.

BNP has no interest in interfering with the FDA’s practice of using the suitability petition to examine issues raised by changes in parenteral drug container sizes. However, that practice should not be permitted to produce, in an entirely different context, unintended results that cannot be justified on their own terms. A de facto denial of exclusivity to BNP’s ANDA for paclitaxel injection 6 mg/ml based on the existence of multiple-dose containers with different fill volumes, a characteristic that has no relevance to product “strength” or any other significant aspect of product identity or pharmaceutical equivalence, would be exactly such a result – surely unintended by those who developed the suitability petition policy, indefensible on technical and regulatory grounds, and unfair to BNP.

If the issue of equating parenteral drug container size with drug “strength” has not been raised with the FDA in the past, it is because, in the suitability petition context, the FDA’s position on the issue has no practical consequences for ANDA applicants: It is not difficult to submit a suitability petition. The time line for developing an ANDA is unaffected by having to submit a suitability petition. And for multiple-dose parenteral drug containers, the outcome of a suitability petition is a predictable grant of permission to file the ANDA. Indeed, it is difficult to hypothesize why the FDA would have any interest in the size of a multiple-dose parenteral drug container, or what the agency staff views as relevant in suitability petitions for different multiple-dose container sizes in terms of any medical or technical issue affecting the “suitability” of an ANDA for a parenteral drug.

In the 180-day exclusivity context, however, an FDA position that each multiple-dose container size is a different drug product would have severe practical consequences for ANDA applicants. In the case of BNP's ANDA, it would confine exclusivity for paclitaxel 6 mg/ml injection to the arbitrary and irrelevant category of 5 ml multiple-dose containers, thereby permitting approval of paclitaxel 6 mg/ml injection in multiple-dose containers that are larger or smaller, but that neither contain a different "strength" of paclitaxel injection nor correspond with a "single-dose" of paclitaxel injection. The most straightforward way of preventing this absurd and unfair outcome is for the FDA to clarify that the definition of "strength" as "total drug content" and the suitability petition policy do not apply to multiple-dose parenteral drug containers.

Accordingly, BNP has submitted the attached citizen petition as the first step in assuring that this issue is resolved in a timely fashion. BNP will be in further communication with your office concerning the agency's schedule for responding to the citizen petition. Please let me know if you need further information. If you have any questions, I can be reached at 305-575-6336.

Sincerely,

Baker Norton Pharmaceuticals, Inc.



Steven M. Viti, Ph.D.
Director, Regulatory Affairs

Enclosure

cc: Jane A. Axelrad
Associate Director For Policy, CDER

Margaret Jane Porter
Chief Counsel

4400 Biscayne Boulevard
Miami, Florida 33137
Telephone: 305-575-6000

December 8, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

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FedEx Tracking Number — PULL UP PURPLE TAB

ORIG AMENDMENT

N/AC

MAJOR AMENDMENT – CHEMISTRY

RE: ANDA 75-184
Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. This submission is a response to the deficiencies noted in the Agency's facsimile correspondence received November 8, 1999 (copy attached). We understand this response is considered a Major Amendment.

Our responses to each of the Office of Generic Drugs comments are presented below, with the deficiencies restated in **bold print**, followed by the response in regular print.

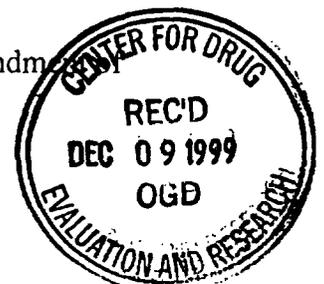
A. Deficiencies

- 1. The DMF for the paclitaxel drug substance remains inadequate. The DMF holder has been notified. Please do not respond until you have been notified that the DMF holder has addressed their deficiencies.**

The DMF holder has notified us that they re-submitted a copy of their DMF response on October 27, 1999. The CSO (Michelle Dillahunt) has confirmed to [redacted] who has confirmed to us, that it has been received.

- 2. In the release specification of the paclitaxel drug substance (page 200107), the manufacturer is [redacted]. However, in the major amendment of April 2, 1999 the [redacted] was the manufacturer of the paclitaxel drug substance for Baker Norton Pharmaceuticals. Please clarify.**

Prior to purchasing active drug substance manufactured by [redacted] Baker Norton Pharmaceuticals purchased paclitaxel drug substance manufactured by [redacted]. At the time the [redacted] drug substance in our major amendment [redacted].



April 2, 1999 (lot 1492-28397A) was released, the _____ specification was the only one in place at Baker Norton. Thus, when Baker Norton tested the _____ material as a possible "alternate source", it was tested against the _____ specification. Since then, we have qualified the material and have written specification _____, which is specific to the _____ material. At this time, _____ is the only active drug substance source in this application.

3. Based on the actual data obtained, please tighten the limit of endotoxin for the release of the drug substance and drug product.

The limit of the bacterial endotoxin test

4. Based on the actual data obtained, please tighten the specification of the total impurities for the paclitaxel drug substance.

Since our original submission, Baker Norton has tested and released 12 additional lots of _____ drug substance. Data for total impurities for all 25 lots of drug substance tested are given in Table 1 below. Total impurities observed to date for 25 lots reached a maximum of _____%. Therefore, we agree to tighten the total impurities specification to NMT _____%. See revised specification provided in Appendix 1.

Following are the Total Impurities results for 25 lots received and tested to date:

Table 1

Lot Number	% Total Impurities (Release)
1321-11597A	
1321-13597A	
1321-05897A	
1321-14897B	
1321-15497A	
1321-17497B	
1321-31996A	
1321-36696A	
1321-22397A	
1492-26997A	
1492-29397A	
1492-27397A	
1321-00297A	
2833-07499A	
2833-08299A	
2833-09699A	
2833-11399A	
2833-12099A	
2833-12599A	
2833-22996A	
2833-24296A	
2833-27597A	
2833-13199A	
2833-28297A	
2833-03296A	

5. **The master batch production formulation on page 300014 is not acceptable. No unit was given for the batch size. The formula of the intended production batch should contain the weight of each ingredient to be dispensed and compounded in addition to the concentration per unit.**

The unit used for the batch size is _____ " This unit is shown on the upper right-hand side of the Product Master Card _____ ; for the 30 mg/5 mL size; for the 150 mg/25 mL size and _____ for the 300 mg/50 mL size). The batch size is indicated as: _____

The Product Master Card _____ indicates _____ for our product (see the upper left-hand side of the _____ under _____ The _____ pack is defined by Faulding as being individual vials. This is covered in Faulding _____

As requested by the Agency, the Product Master Card has been revised to contain the weight of each ingredient to be dispensed for each batch in addition to containing the concentration per unit. The revised Product Master Cards for each size are presented in Appendix 2:

	Issue #009
	Issue #009
	Issue #003

6. **In the bulk formulation of the paclitaxel injection concentrate, 30 mg/5mL (p. 300014), 150 mg/25mL (p. 100162), 300 mg/50mL (p. 100235) the “alternative” paclitaxels have different code numbers from the paclitaxel. In addition, they are to be used for adjusting the potency. Please explain.**

The product master card, BRF000 lists the various sources of paclitaxel active drug substance which we have used over the years. As explained in our response to Comment #2 above, prior to purchasing active drug substance from Baker Norton Pharmaceuticals purchased paclitaxel drug substance from other companies, including [redacted] is no longer a viable source and has since been deleted from the product master card).

All sources are segregated by codes:

[redacted] denotes paclitaxel active drug substance manufactured by [redacted]
 [redacted] Faulding Code 200091 denotes active drug substance manufactured by [redacted]
 [redacted] and [redacted] denotes active drug substance manufactured by [redacted]

Company policy for both Baker Norton Pharmaceuticals and for Faulding Pharmaceuticals prohibits the mixing of different active drug substance sources in a single batch of product. The sources are not interchangeable nor are they used to adjust the potency. Please also note that no paclitaxel overage is used in the formulation of this product, as indicated in the upper right-hand corner of the Product Master Card (“ADS Overage %: Nil”). At this time [redacted] is the only active drug substance source in this application.

7. In the executed batch records (pages 100162, 100238, 400102, 400123), it appeared that paclitaxel code #200091 was used interchangeably with code #200090. Please provide the specifications and the source of suppliers for all grades of paclitaxel raw materials including code number 210500 listed as "alternative".

As explained in our response to Comment #6 above, the sources of active drug substance are never used interchangeably. _____ denotes active drug substance manufactured by _____ and this code appears consistently throughout all batch record documentation for the three batches submitted, 8016858, 8026859, and 8016861:

Page 100162	Batch 8026859:
Page 100163	Batch 8026859:
Page 100238	Batch 8016861:
Page 100260	Batch 8016861:
Page 400102	Batch 8016858:
Page 400123	Batch 8016858:

At this time, _____ is the only active drug substance source in this application.

8. In the executed batch record (pages 400102, 400123), under change required, No.3 "Reduce batch size from _____ singles to _____ singles". Please explain.

The existing manufacturing batch record is for a _____ liter commercial size batch requiring _____ grams of active raw material. However, for this exhibit batch, a change was executed to the master batch record to scale down the batch size to _____ liters, approximately half the commercial size. The theoretical yield of vials was also reduced accordingly; and the specific instructions to reduce to _____ singles took into consideration overfill of each vial plus line loss which for this non-aqueous formulation was calculated at approximately _____ liters.

9. The revised formulation of the Paclitaxel Injection 6 mg/mL is sterile nonaqueous solution. However, the limit of the moisture content is increased to % for the release of the drug product. Please explain.

The revised formulation is comprised of approximately % Cremophor EL and approximately % Dehydrated Alcohol:

Ingredient	Quantity per mL	Quantity per Batch
✓ Paclitaxel	✓ 6 mg	g
✓ Polyoxyl 35, Castor Oil, NF	✓ 527 mg	Kg
✓ Citric Acid, Anhydrous, USP	✓ 2 mg	g
✓ Dehydrated Alcohol, USP	✓ 49.7% (v/v)	L

Polyoxyl 35, Castor Oil, NF (Cremophor EL) has a moisture limit of % (per USP). Since it comprises almost % of the formulation, the Cremophor EL alone can contribute as much as % moisture to the final formulation. Although the alcohol is dehydrated and has negligible moisture content (as is the case with the paclitaxel active drug substance and the citric acid), it does have the propensity for picking up moisture during formulation.

Following is a table showing moisture value on 14 lots of Paclitaxel Injection we have manufactured to date using this same formulation:

Table 2

Batch Number	Moisture Value
5206858	%
5216858	%
6016858	%
6046858	%
6066858	%
6076858	%
7016858	%
7026858	%
7016860	%
7036858	%
7036859	%
8016858	%
8026859	%
8016861	%
Average/14 Lots:	%

Note: boldface = exhibit batches in this application

Moisture values for this formulation have historically ranged from % to a high of %. Based on this historical data and on the formulation characteristics mentioned above, we have set the moisture specification for the product at what we consider to be a safe and realistic level of %, which is borne out by long-term stability data for the above lots.

10. The microbial limit test for the absence of salmonella species, E. coli, staphylococcus aureus, and pseudomonas aeruginosa was eliminated for the drug substance. Please explain.

At release of each lot, the drug substance manufacturer, performs the microbial limit test for the absence of salmonella species, E. coli, staphylococcus aureus, and pseudomonas aeruginosa. Certification is provided to Baker Norton. Upon receipt of the active drug substance, BNP samples and performs analytical testing as well as testing for Total Plate Count and Bacterial Endotoxins. Due to the cytotoxic nature of the drug and the accuracy of the microbial testing, Baker Norton does not deem it necessary to test again for the absence of salmonella species, E. coli, staphylococcus aureus, and pseudomonas aeruginosa.

11. System suitability tests should be performed to verify that the resolution and reproducibility of the chromatographic system are adequate.

For the method system suitability is performed to verify that the resolution criteria of the method are met, as recorded in Section 3 (page 6) of the method. Please see page 100018 of our April 2, 1999 amendment (page 7 of 12), System Suitability Criteria. This demonstrates that the RSD of the Standard Response Area must be less than 2% (for Reproducibility) for the paclitaxel peak. As can be seen from page 7 of the method (Criteria), five different system suitability criteria, including resolution and reproducibility, are performed.

For method page 5 of 9 (System Suitability test) shows that the system suitability test is performed to verify that the resolution and reproducibility of the chromatographic peaks are adequate. This is described on page 100134 of our April 2, 1999 amendment.

12. In the report of system suitability test for the method validation (Supplement 1), the specification of the resolution factor NLT is not acceptable. Please adjust the limit to ensure that closely eluting compounds are resolved from each other.

Based on a review of the data, we will adjust the specification of the resolution factor from NLT to NLT in . This will assure the best resolution this method is capable of demonstrating.

Attached in Appendix 3 is a chromatogram demonstrating sufficient resolution of the leading peak to paclitaxel at . We believe this chromatogram demonstrates there is still some margin of safety and that a resolution of on the leading peak should be acceptable. Please note that the proposed USP monograph in the Pharmacopeial Forum (also provided in Appendix 3) also indicates a resolution factor of NLT for Impurity B

- 13. In the report on paclitaxel stability in various intravenous solutions (pages 600260-600291), the storage conditions were given as “refrigerated and room temperature conditions”. Please specify the actual temperatures for your studies.**

The actual temperature for the studies under refrigerated conditions is °C and at room temperature is approximately °C.

- 14. Please demonstrate that the anhydrous citric acid acts as a buffer (exception excipient) in your non-aqueous formulation of paclitaxel injection.**

Paclitaxel Injection has been demonstrated to be sensitive to base hydrolysis and stable to acidic conditions. Therefore, the use of the citric acid as a buffer is to prevent base hydrolysis. The experiment described below demonstrates this buffering capacity. A similar experiment was also performed for acid titration and showed similar results. These results, however, will not be presented as they are not considered necessary in responding to this question.

In order to demonstrate the buffering capacity of citric acid in this formulation it is necessary to show that the inclusion of citric acid reduces the change in pH per milliliter of base relative to a non-citric acid sample. Therefore, it was necessary to prepare two Paclitaxel Injection solutions, one with and one without citric acid. The two Paclitaxel Injections solutions were prepared and then diluted to % in water to facilitate the titration process.

The two aqueous solutions were titrated with 0.1N NaOH. Table 3 and Figure 1 both clearly demonstrate that the change in pH resulting from the addition of the base is much slower for the citric acid formulation than for the non-citric acid formulation. The addition of approximately milliliter of base increases the pH of the non-citric acid solution units while the same amount of base only increases the pH of the citric acid solution units

This buffering affect is sufficient to demonstrate that the inclusion of citric acid serves as a buffer in this formulation.

Redacted 1

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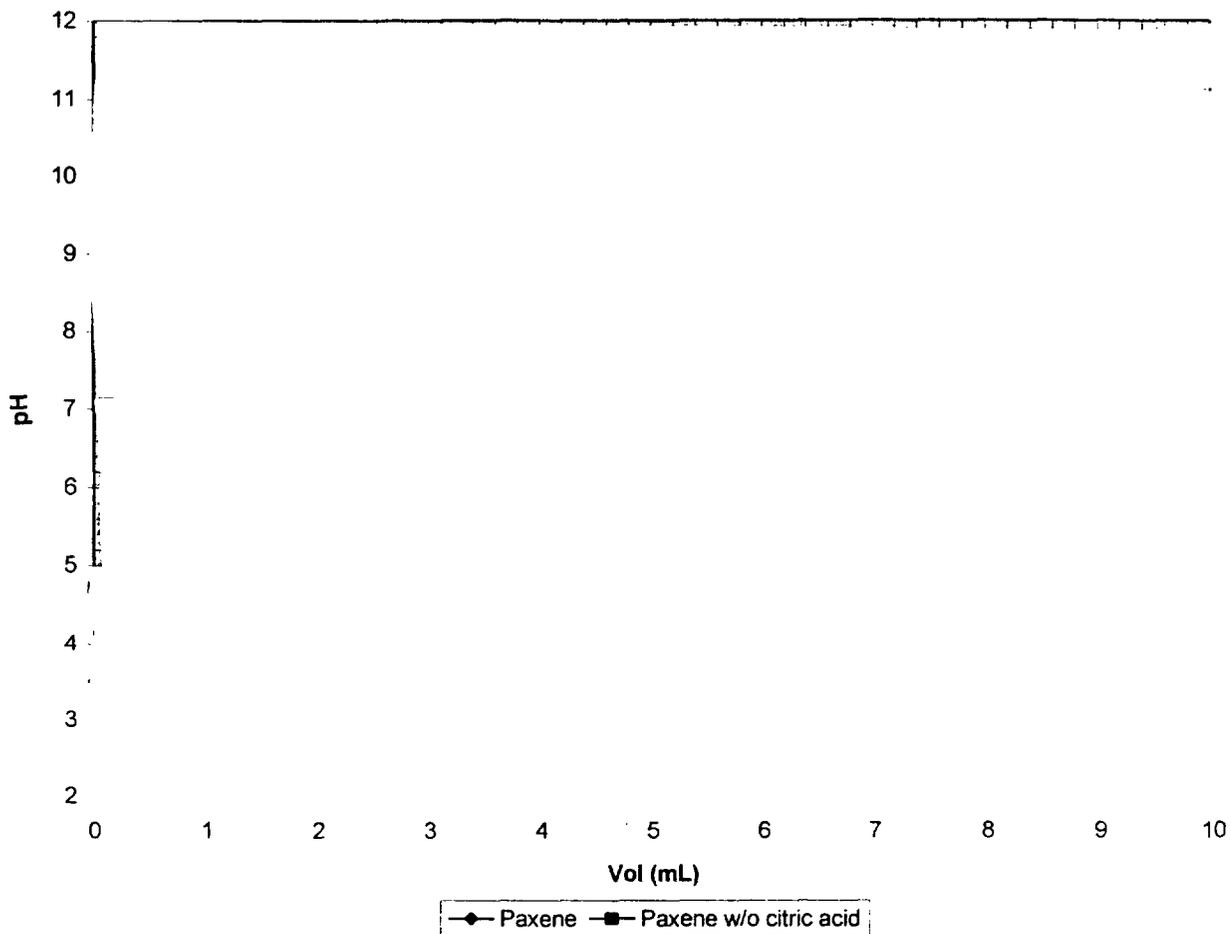
confidential

commercial

information

Figure 1

Basic Titration 0.1 N NaOH



15. In your executed batch record (8026859), on page 100162, the batch size appears to be (the number got cut off this photocopy) vials of 150mg/25mL. Please explain how the batch size vials related to the rest of the calculations. For example, how much of active is required to be dispensed for this batch size.

The commercial batch record is for liters, which has a theoretical yield of vials of the 150 mg/25 mL size after rejects, in-process samples, retention samples, etc. The number is the standard unpacked singles – the number of vials that will need to be filled to yield at least vials.

Exhibit batch 8026859 was manufactured from approximately _____ grams active drug substance; thus the commercial (master) batch record was scaled down accordingly. Calculations and their relationship follow:

Component	Theoretical Quantity: Commercial Batch Size _____ liters, containing _____ grams ads)	Theoretical Quantity: Exhibit Batch 8026859 (containing _____ grams ads)	Actual Quantity: Exhibit Batch 8026859
✓ Paclitaxel active drug substance	_____ grams	_____ grams	_____ grams
✓ Polyoxyl 35, Castor Oil NF (Cremophor EL)	_____ Kg	_____ Kg	_____ Kg
✓ Citric Acid, Anhydrous, USP/BP	_____ grams	_____ grams	_____ grams
✓ Dehydrated Alcohol, USP	_____ liters	_____ liters	_____ liters
Theoretical Yield (vials)		_____ vials	_____ vials

A more legible copy of Page 100162 from our June 15, 1999 amendment is presented in Appendix 4.

16. Three pages (p. 1000163-100165) in the amendment of June 15, 1999 show handwritten changes for every item. Please explain the meaning of each number.

The method of formulation that was followed at the time that Batch 8026859 was manufactured required that

_____ Due to a miscalculation which resulted in an in-process out-of-specification result, the amounts of excipients were changed on more than one occasion.

We no longer use this method of formulation. As requested by the Agency and as indicated in our response to Comment #5 above, the master batch record has been revised to specify the theoretical quantity of each ingredient to be used per batch. We present in Appendix 2 the revised batch record documentation: _____ for each fill size, specifying the amount of each ingredient to be used for each batch; and _____ which specifies the amounts and documents the addition of each ingredient to the batch.

17. The use of paclitaxel overage is not acceptable. Your manufacturing instructions for the adjustment of paclitaxel drug substance are inappropriate. Please revise and remove the adjustment for paclitaxel.

No overage of paclitaxel is used. Batch Record Form for Mixing has been revised to reflect the exact amount of each ingredient to be added to the bulk solution (see revised Issue #9, contained in Appendix 2). The notation of adjusting the paclitaxel for potency and moisture content refers to adjusting the amount of paclitaxel raw material to be used in the bulk mix prior to mixing, to compensate for shortfalls in potency caused by moisture content or an anhydrous potency of less than % . This is to ensure that the equivalent of % anhydrous active is added to the mix. This statement does not refer to in-process potency adjustment to the bulk mix.

18. No weighing records were found for the executed batch #8016861 of the Paclitaxel injection, 300 mg/50mL. Please explain.

The Dispensing list ("Pick Sheet") in the batch record shows that the following amounts were dispensed for this 42-liter exhibit batch, 8016861:

Ingredient	Amount Dispensed	Page Number
Paclitaxel Active drug substance manufactured by	grams	Page 100260
Polyoxyl 35, Castor Oil, NF (Cremophor EL)	kg	Page 100260
Citric Acid , Anhydrous, USP	grams + grams	Page 1000260
Dehydrated Alcohol, USP	kg	Page 100262

19. Please explain the calculations and changes of weights on page 100260, paclitaxel injection 300 mg/50mL (batch No. 8016861).

Please refer to Response #16. The changes were a result of a procedure in practice at the time. The procedure is no longer used for product manufacture, therefore changes are eliminated in future batch records.

20. Regarding the analytical methods of

Please clarify.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

- 1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval.**

Baker Norton acknowledges that the firms referenced in this application must be in compliance with cGMPs at the time of approval.

- 2. The FDA district office will be performing method validation on the finished drug product, Paclitaxel Injection, concentrate.**

Samples of the drug product lots in this application (8016858, 8026859 and 8016861) are available at Baker Norton Pharmaceuticals, 8800 NW 36th Street, Miami, FL 33178 and will be submitted upon request.

- 3. The microbiology review has not been completed. Review comments, if any, will be transmitted at a later date.**

We acknowledge that the microbiology review has not been completed and that any review comments will be transmitted at a later date.

- 4. The review for the environmental impact assessment has not been completed. Any deficiencies found will be communicated to you under a separate cover.**

We acknowledge that the environmental impact assessment has not been completed and that any deficiencies found will be communicated to us under separate cover.

- 5. Regarding the amendment dated June 15, 1999, page 100162 is illegible. Please replace with a legible page.**

A more legible copy of page 100162 from our submission dated June 15, 1999 is provided in Appendix 4, where the information on the upper right-hand side of the page (your Comment #15) is complete. Also provided in Appendix 4 is the implemented copy of this document, which clearly shows all information on the left-hand side of the page.

- 6. An error needs to be corrected on page 100383. "The total percent impurities increased from % at initial and ranged from % from 1-3 months at accelerated conditions."**

The error has been corrected. Please see revised page provided in Appendix 5.

7. Please provide all available long-term stability data.

Long-term stability data is provided in Appendix 6 for the following exhibit batches:

Lot #	Storage Conditions	Testing Time Points Submitted Here
8016858 (30 mg/5 mL)	% RH, Inverted	0, 3, 6, 9, 12, 18
8016858-OC* (30 mg/5 mL)	% RH, Inverted	0, 3, 6, 9, 12, 18

Testing is already complete and has previously been submitted for the following batches:

Lot #	Storage Conditions	Testing Time Points Previously Submitted
8016858 (30 mg/5 mL)	% RH, Inverted	0, 1, 2, 3, 6 – Complete
8016858-OC* (30 mg/5 mL)	% RH, Inverted	0, 3, 6 – Complete

*These batch numbers represent a portion of the submission batch which was packaged with [

Testing is currently in progress for the following lots and will be submitted to the Agency as soon as it is available:

Lot #	Storage Conditions	Testing Time Points Previously Submitted
8026859 (150 mg/25 mL)	% RH, Inverted	0, 1, 2, 3
8016861 (300 mg/50 mL)	% RH, Inverted	0, 1, 2, 3
8026859 (150 mg/25mL)	% RH, Inverted	0, 3
8016861 (300 mg/50 mL)	% RH, Inverted	0, 3

Labeling Deficiencies:

Our response to labeling deficiencies from the April 2, 1999 and June 15, 1999 submissions will be submitted under separate cover.

Baker Norton Pharmaceuticals has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions or require additional information please contact our office at your convenience at (305) 575-6336.

Sincerely,
Baker Norton Pharmaceuticals, Inc.



Steve Viti, Ph.D.
Director, Regulatory Affairs

December 9, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ND- DRUG AMENDMENT
N/A F

MAJOR AMENDMENT - LABELING

RE: ANDA 75-184
Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL vial and 300 mg/50 mL

Dear Mr. Sporn:

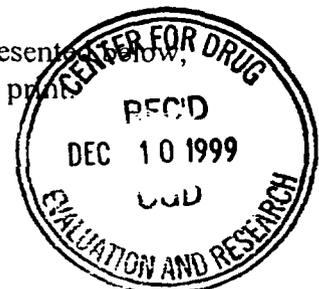
Reference is made to our pending abbreviated new drug application for Paclitaxel Injection, 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. This submission is a response to the deficiencies noted in the Agency's facsimile correspondence received on November 8, 1999 (copy attached). A response to the Chemistry questions was provided under separate cover to facilitate review. We understand this response is considered a Major Amendment.

We have updated the Baker Norton labeling to the most current Taxol labeling approved on October 25, 1999. This labeling includes approval for adjuvant treatment of node-positive breast cancer for which Bristol-Myers has received exclusivity. We have previously acknowledged in a letter to the Agency dated June 30, 1999 the exclusivities granted for:

- 1) Second line treatment of AIDS-related Kaposi's sarcoma,
- 2) First-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin. We are, however, seeking approval for *subsequent* therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin
- 3) Paclitaxel Injection in combination with cisplatin for first line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy, and
- 4) Orphan drug status.

We are amending our application for Paclitaxel Injection with a new Exclusivity Statement to include the newest indication of adjuvant treatment of node-positive breast cancer. The labeling has been updated accordingly. The four indications are deleted from the proposed labeling and revised final draft labeling is provided in this submission.

Our response to each of the Office of Generic Drugs labeling comments are presented below, with the deficiencies restated in bold print, followed by the response in regular print.



Labeling Deficiencies:

1. CONTAINER (5mL, 25mL, and 50mL)

a. Satisfactory.

No container labeling provided based on satisfactory comment.

2. CARTON (1 x 5 mL, 1 x 25 mL, and 1 x 50 mL)

a. Satisfactory.

No carton labeling is provided based on satisfactory comment.

3. INSERT

- a. Please note that the most recent labeling for the reference listed drug, TAXOL®, was approved January 8, 1999. Multiple supplements were approved at that time, and it should be noted that S-031 is subject of an exclusivity for “use in combination with cisplatin, for the 1st line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation”. We have enclosed a copy of this labeling. Please revise your insert accordingly.**

The package insert has been revised according to the most recent labeling approved October 25, 1999 for the reference listed drug, Taxol. The exclusivity denoted by S-031 has been omitted from the labeling. Four (4) copies of revised draft insert labeling are provided.

b. BOXED WARNINGS

- i. Revise the first sentence of paragraph three of this section to read as follows:**

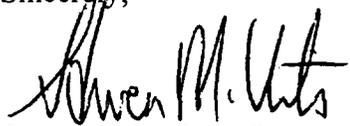
...than 1500 cells/mm³ and should not be given to patients with AIDS-related Kaposi’s sarcoma if the baseline neutrophil count is less than 1000 cells/mm³.

The statement is not applicable as Kaposi’s sarcoma is not a labeled indication in this application.

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Should you have any questions or require additional information please contact me at (305) 575-6336 (phone) or via fax at (305) 575-6339.

Sincerely,


Steven M. Viti, Ph.D.
Director, Regulatory Affairs

ORIG AMENDMENT
MAF

ANDA 75-184
GRATUITOUS AMENDMENT - LABELING

January 26, 2000

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Paclitaxel Injection, 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL
Multiple Dose Vials

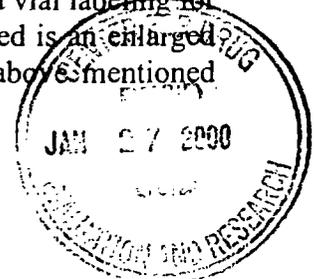
Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 150 mg/25 mL and 300 mg/50 mL. On December 9, 1999, Baker Norton responded with a Major Amendment to the Agency's facsimile correspondence received November 8, 1999.

Baker Norton is amending its December 9, 1999 Major Amendment by submitting this Gratuitous Amendment. This amendment provides for a change in reference to the name of the finished product as it appears on the labeling (cartons, vial labels and insert). The only difference between this revised labeling and previous labeling (12/09/99) is reference to the name of the drug. The BNP revised insert, cartons and vial labeling now refers to the product by its BNP brand name **Paxene® (paclitaxel) Injection**. On the package insert, the name paclitaxel is retained in areas where the drug is cited in reference to clinical studies.

It is our intention for the labeling be reviewed in conjunction with our Major Amendment dated December 9, 1999, and be treated as one complete Amendment. We acknowledge that our Major Amendment of December 9, 1999 provided a package insert, carton and vial labeling for the 30 mg/5 mL, 150 mg/25 mL and the 300 mg/50 mL strengths.

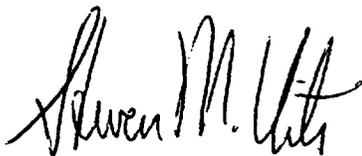
Included in this submission are 4 copies of the revised package insert, carton and vial labeling for the 30 mg/5mL, 150 mg/25 mL and the 300 mg/50 mL strengths. Also included is an enlarged version of the package insert and the side by side comparisons for all the above mentioned



components and strengths. Besides the reference to the brand name **Paxene[®] (paclitaxel) Injection** the strengths presented here are similar in content and format to that previously submitted on December 9, 1999.

Baker Norton Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to call me at (305) 575-6336.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven M. Viti". The signature is fluid and cursive, with the first name "Steven" being the most prominent.

Steven M. Viti, Ph.D.
Director, Regulatory Affairs
Baker Norton Pharmaceuticals, Inc.